The Management of Eosinophilic Esophagitis

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Activity Objectives

1. Be able to identify the symptoms associated with eosinophilic esophagitis and when to initiate work-up of such patients.
2. Understand the histologic features of eosinophilic esophagitis.
3. Understand the approaches to dietary and medical management of eosinophilic esophagitis.
4. Identify the allergist's role in the management of eosinophilic esophagitis.

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Abbreviations used
APT- Atopy patch test
EGD- Esophagogastroduodenoscopy
EoE- Eosinophilic esophagitis
FP- Fluticasone propionate
GERD- Gastroesophageal reflux disease
GI- Gastrointestinal
HPF- High-powered field
Ig- Immunoglobulin
NLR- Negative likelihood ratio
NPV- Negative predictive value
OCS- Systemic oral corticosteroids
OVB- Oral viscous budesonide
PLR- Positive likelihood ratio
PPI- Proton pump inhibitor
PPIRee- Proton pump inhibitor—responsive esophageal eosinophilia
PPV- Positive predictive value
PST- Prick skin test
QoL- Quality of life
SFED- "6 food" elimination diet
TCS- Topical corticosteroids
TGF- Transforming growth factor
TIGERS- The International Group of Eosinophil Researchers

Eosinophilic esophagitis (EoE) is a clinicopathologic, chronic esophageal inflammatory disease resistant to acid suppressive therapy and is associated with variable symptoms indicative of upper gastrointestinal dysfunction. Per current guidelines established by The International Group of Eosinophil Researchers (TIGERS), the diagnosis is made in symptomatic patients after a biopsy that confirms a peak eosinophil level of ≥15 eosinophils/high-powered field (HPF). The esophagus is distinguished by pronounced tissue eosinophilia in which dietary antigens are key inciting factors for disease pathogenesis; EoE being reversed by elimination of triggering food allergens suggests that the disease is mediated in part by allergic sensitization to foods. Moreover, experimental EoE in mice can be induced not only via food exposure but also via aeroallergen exposure. Consistent with an allergic etiology rather than an acid-induced esophagitis, swallowed glucocorticoids are effective for the treatment of EoE. Evaluation by an allergist is a recommended part of the diagnostic workup, especially for management of allergic comorbidities. Clinical practice for the evaluation of patients with EoE mainly relies on prick skin tests due to the ease and validation of these tests in the context of immediate hypersensitivity. However, both atopy patch testing and serum IgE testing have been used in EoE. Herein, we reviewed the basic clinical features of EoE with a focus on the approach to diagnosing causative food allergens and to dietary therapy. **(J Allergy Clin Immunol: In Practice 2013;1:332-40)**

Key words: *Eosinophilic esophagitis; Eosinophil; Dietary management; Empiric diet; Six-food elimination diet; Elimination diet; Targeted elimination diet; Elemental diet; Skin testing; Atopy patch testing; Swallowed steroid therapy*

Eosinophilic esophagitis (EoE) is a chronic, Th2-inflammatory esophageal clinicopathologic condition driven in part by food antigens. Per current guidelines established by The International Group of Eosinophil Researchers (TIGERS), the diagnosis is made in symptomatic patients after a biopsy that confirms ≥15 eosinophils/high-powered field (HPF), at a minimum of at least one esophageal level (eg, distal, proximal), in whom acid reflux has been ruled out.[1] Clinical symptoms are variable and differ by age.[1,2] Associated esophagogastroduodenoscopy findings may include numerous gross visual and microscopic changes (Table I), although the esophagus can appear grossly normal. However, these other features are insufficient for diagnosis, and no symptom pattern is diagnostic of EoE. Comorbidities such as other atopic diseases and gastroesophageal reflux disease (GERD) are often present; although GERD can coexist with EoE, the esophageal eosinophil threshold of ≥15 eosinophils/HPF should hold even when acid is blocked[1,3]

TABLE I. Common gross and histologic features of EoE

Gross visual features	Microscopic features
Longitudinal furrows	Basal zone hyperplasia
Felinization (rings)	Eosinophilic microabscesses
White exudates/plaques	Eosinophil surface layering
Nodules	Degranulated eosinophils
Narrowing/narrow caliber	Rete peg elongation
Erosion/laceration/ulceration	Dilated intracellular spaces
Renting/tearing	Subepithelial lamina propria fibrosis

EoE, Eosinophilic esophagitis.

Esophageal eosinophilia, as a syndrome, was first described in the late 1970s, and, whereas EoE has been present for decades as a clinical entity, it was poorly recognized until the 1990s.[4,5] EoE appears to disproportionally affect non-Hispanic, white, atopic males, with a 3:1 male-to-female ratio, and EoE onset occurs in childhood or in the third or fourth decade of life.[1,6] Incidence rates range between 0.7 and 10 per 100,000 per person-year, and prevalence rates range from 0.2 to 43 per 100,000.[7-9] Results of several studies have demonstrated a treatment role for both diet and corticosteroids and a likely allergic mechanism supported by evidence that notes overexpression of key Th2 cytokines and allergic inflammatory cells, including eosinophils, mast cells, IL-5, IL-13, and eotaxin-3.[1] Eotaxin-3 single-nucleotide polymorphisms are present in 14% of cases, and researchers have identified an "EoE transcriptome," a unique set of approximately 1% of the genome that is overexpressed in patients with EoE.[6] A genome-wide association study identified a disease susceptibility locus at 5q22, which harbors the gene for thymic stromal lymphopoietin, and candidate gene analyses have identified genetic polymorphisms in thymic stromal lymphopoietin and its receptor that are associated with EoE susceptibility.[10,11] In addition, overrepresentation of filaggrin mutations, unrelated to the presence of atopic dermatitis, is present in patients with EoE.[12] Interestingly, up to 25% of all known cases of EoE may not be atopic, as defined by the lack of allergic sensitization on testing.[1]

PATIENT EVALUATION

Patients with suspected EoE benefit from evaluation from both allergy and gastroenterology services, and management is often shared. The role of esophagogastroduodenoscopy and esophageal biopsy is essential, as is having a pathologist experienced with reading these biopsy samples, because the diagnosis of the disease requires microscopic evaluation of esophageal biopsy

TABLE II. Comparison of patient-reported EoE symptoms, by age

Symptom	Children*	Teenagers	Adults
Failure to thrive	X		
Difficulty feeding/food refusal	X		
Vomiting	X	X	
Gastroesophageal reflux	X	X	X
Abdominal pain	X	X	X
Chest pain		X	X
Dysphagia		X	X
Overchewing food		X	X
Overcutting food		X	X
Impaction		X	X

EoE, Eosinophilic esophagitis.
*Additional symptoms may be suspected but not verbalized.

samples.[1,3] Age-related symptoms are detailed in Table II. Although substantial esophageal eosinophilia is sometimes found in asymptomatic individuals, the significance of this incidental esophageal eosinophilia is uncertain, and these patients are often managed as having EoE. There is a trend toward a family history of similar symptoms, typically attributed to gastroesophageal reflux disease (GERD), and very often adults may go undiagnosed for years, despite symptoms.[2] Some providers have observed seasonal fluctuations of symptoms and histology.[2] Esophageal eosinophilia associated with GERD is typically 0-5 eosinophils/HPF, but higher levels can also be seen, up to 60 eosinophils/HPF.[13-15] Patients with suspected EoE should undergo an 8-week trial of daily proton pump inhibitor (PPI) therapy before the biopsy to rule out the possibilities of GERD or a PPI-responsive esophageal eosinophilia (PPIRee).[1,3] Typically, eosinophilia that results from GERD lacks some of the other typical histologic abnormalities (eg, microabscesses, surface layering), although no symptom or histopathologic findings absolutely differentiate the conditions.[16-20] Although the cutoff of $\geq$15 eosinophils/HPF is presently recommended, this level is not absolute, and strong suspicion of EoE should remain for symptomatic patients on PPI therapy despite counts below this threshold.

MANAGEMENT OF EOE

There are two general types of management options in clinical practice for the majority of patients with EoE: the use of dietary elimination or topical corticosteroids. However, there are no current data from randomized, controlled studies to provide guidance as to the superiority of one particular approach. Combination therapy is a third option. All options should include consideration of adjunctive use of PPI. Biologic therapies are investigational and show potential promise but are not recommended for clinical use. The principles of treatment should focus on reducing symptoms, biopsy-based eosinophil counts, and associated histologic and visual endoscopic changes while protecting and preserving quality of life (QoL) and nutrition.[1]

Steroid treatment of EoE

Corticosteroids increase eosinophil apoptosis, downregulate eosinophil chemotaxis, and inhibit proinflammatory cytokines that promote eosinophil survival and activation.[21-25] Systemic oral corticosteroids (OCS) can induce remission of EoE symptoms and both gross and histologic features at doses of 1-2 mg/kg. OCS are limited by the long-term steroid adverse effects and relapse after discontinuation but have exceptional benefit in a subset of severely symptomatic patients or patients with critical strictures.[26,27] Topical corticosteroids (TCS), either swallowed oral viscous budesonide (OVB) or gulped actuations of fluticasone propionate hydrofluoroalkane (FP) via metered dose inhaler, are the preferred steroid treatment in EoE. TCS provide "local" topical targeting of esophageal tissue as indicated by modulation of esophageal gene expression, including induction of steroid-responsive genes in the esophagus.[28] Results of numerous studies have demonstrated TCS efficacy in children and adults.[29-33] OVB decreases eosinophil counts and reverses fibrosis and/or remodeling, TGF-β1, and phosphorylated SMAD 2/3 in pediatric EoE biopsy samples.[34-36] It is possible that OVB could influence smooth-muscle contraction, which is induced by TGF-β1 *in vitro*. A CC-509 gene polymorphism in the TGF-β1 promoter is associated with a better TCS response.[34-36] Short courses of OVB (15 days) in adults have reduced both symptoms and eosinophil counts, as have prolonged courses in adults at a low, daily maintenance level.[37,38] There are no guidelines for optimal duration of TCS treatment or adequate maintenance and/or chronic therapy, although short courses are associated with higher rates of relapse.[39] Many experts believe that, because the disease is chronic, persistent, and prone to relapse, long-term therapy may be indicated.[1] No long-term safety data exist that pertain to swallowed dosing methods used in EoE.

Acid suppression

Acid suppression in EoE is a complementary therapy for EoE. An 8-week PPI regimen is very strongly recommended before the diagnostic biopsy to control for the presence of comorbid reflux and associated esophageal eosinophilia.[1,3] Some researchers advocate that a PPI trial is a firm diagnostic requirement.[40] High-dose PPI therapy before a biopsy is thought to help differentiate low-grade esophageal eosinophilia indicative of reflux. Patients who respond are thought to be indicative of possible PPIRee, an evolving concept.[1] However, symptom response on high-dose PPI therapy correlates poorly with histology.[13,14,41-43] PPI therapy does have anti-inflammatory effects, such as inhibition of IL-4–stimulated eotaxin-3 expression through blocking of STAT-6 at the eotaxin promoter, suggestive of how it may help reduce eosinophils.[44] In a murine asthma model, as well as in human samples, an acidic microenvironment increases eosinophil survival and eotaxin-3 cellular release.[12,45] Beyond the experts' opinion that a PPI trial is necessary to rule out PPIRee, PPI therapy may also provide important symptomatic relief for some patients. Controlled trials would be helpful to better clarify the specific role for prebiopsy use of PPI.

Dietary management

There is evidence that supports the role of dietary antigens in EoE pathogenesis, including favorable adult and pediatric evidence that the disease is treatable through dietary elimination by using amino acid–based (elemental) diets, targeted elimination diets, or empiric (6-8–food) elimination diets. Reintroduction of specific foods is frequently associated with disease recurrence. Evidence even exists that dietary treatment can benefit those without positive skin tests or individuals in whom such evaluation was never undertaken.[1]

TABLE III. Comparison of food prick skin testing and atopy patch testing precision in patients with eosinophilic esophagitis

	Prick skin testing precision				Atopy patch testing precision			
Food	Sensitivity	Specificity	NLR*	PLR*	Sensitivity	Specificity	NLR*	PLR*
Milk	26.6	87.8	0.84	2.18	29.9	87.0	0.81	2.30
Egg	70.0	85.8	0.35	4.92	48.8	91.4	0.56	**5.70**
Soy	40.4	82.1	0.73	2.25	52.5	86.7	0.55	3.95
Wheat	18.1	87.4	0.94	1.44	57.1	81.8	0.52	3.14
Peanut	88.2	88.4	**0.13**	**7.61**	60.0	92.6	0.43	**8.15**
Corn	30.6	91.5	0.76	3.60	92.1	86.7	**0.09**	**6.91**
Beef	45.7	92.3	0.59	**5.90**	55.6	89.1	0.50	**5.11**
Chicken	55.9	89.5	0.49	**5.31**	68.0	88.0	0.36	**5.67**
Rice	13.3	97.5	0.89	**5.32**	86.7	87.5	**0.15**	**6.93**
Potato	42.1	97.0	0.60	**14.00**	69.2	91.3	0.34	**7.93**
Pork	29.4	95.4	0.74	**6.34**	47.1	89.6	0.59	4.51

NLR, Negative likelihood ratio; *PLR*, positive likelihood ratio.
*Values in bold type represent a NLR of <0.20 or less or a PLR >5.00, which, when applied to the pretest probability of having the disease can estimate the posttest probability of the disease. All values in the table are from reference 51 except rice, which are from reference 48; these data are exclusively from a pediatric population, and these values may not be applicable in adult populations.

Elemental dietary therapy. Kelly et al[46] demonstrated that a 6-week trial of elemental formula in 10 pediatric patients with esophageal eosinophilia resulted in complete histologic and symptomatic resolution in eight subjects and a partial improvement in the remaining two subjects, although all the patients relapsed with diet discontinuation. In a larger pediatric study, Markowitz et al[47] noted symptomatic response by 8 days and biopsy sample normalization by 1 month in 49 of 51 patients treated with elemental diet. Liacouras et al[48] noted a 97% response rate to elemental diet in a 10-year longitudinal study of 160 pediatric patients with EoE. Adults have responded histologically to elemental dietary therapy, but adherence was low, and symptoms did not improve.[49] Thus, elemental therapy may be less appropriate in older children, adolescents, or adults. Some patients require placement of a gastrostomy tube to assist with elemental feeding; formula taste has been cited as influencing poor compliance.[50] There are no long-term studies of the effectiveness of an elemental diet in EoE, nor its impact on QoL.[1]

Targeted dietary elimination. An alternative approach to elemental diet is a targeted elimination diet, whereby specific foods are avoided on the basis of food allergy testing and known food sensitizations. Spergel et al[51,52] identified the 13 most common pediatric food triggers through a combination of prick skin test (PST), atopy patch test (APT), directed elimination and single-food add-back with follow-up endoscopy. These investigators studied 120 pediatric patients with EoE placed on a 6-8—week testing-guided elimination diet; 112 of 120 achieved near-complete remission, although 39 relapsed upon reintroducing eliminated foods. The investigators noted that most patients were multisensitized but that 77% had at least 1 positive PST, and 85% had 1 positive APT. On the basis of the add-back, positive predictive value (PPV) (50%-92%) and negative predictive value (NPV) (>88%, except milk) were established (sensitivity >77%, specificity >82%, except milk and apple).[52,53] However, other groups have noted difficulty in replicating these data.[54,55] Molina-Infante et al[54] demonstrated poor effect of targeted elimination in 22 adult patients with EoE. PST (including use of fresh food) and APT were used to guide elimination for 6 weeks in 15 patients, with only 4 of 15 achieving complete remission (<5 eosinophils/HPF), 1 of 15 achieving partial remission (5-15 eosinophils/HPF), and 10 of 15 having no change. Among patients who either refused the diet, did not respond to the diet, or had negative testing, 14 of 17 achieved complete remission on 6 weeks of swallowed FP.[54] However, this study was limited because of a small sample size and lack of randomization and a control group.

In general, PST in EoE has good specificity (>82%) but poor sensitivity (18%-88%), with positive likelihood ratios (PLR) in excess of 2 and negative likelihood ratios (NLR) below 0.85 (except for wheat in both cases), which indicates usefulness of both positive and negative tests.[53,56] Because EoE has a non-IgE—mediated mechanism, APT to assess delayed hypersensitivity—mediated reactivity to foods has been advocated.[51,52] The specificity of APT is similar to PST, but sensitivity, PLR (2.30-8.15), and NLR (0.81-0.09) are noticeably superior (Table III).[53] Allergen testing in patients without biopsy-proven EoE lacks validity because test precision is tightly tied to disease presence. There is no established role for allergy serologic testing presently.[1] The greatest advantages of the targeted approach is that it can help preserve nutrition and dietary normalcy through limiting elimination and that the high NPV/NLR from the combined PST/APT can help guide dietary readditions after elimination. Criticisms include that the data are based on a predominantly pediatric sample, which may not generalize to an adult population; certain food tests (milk, wheat) have poor reliability; the APT process is not standardized; APT interpretation is highly subjective and variable; and the data are poorly reproducible.

Empiric dietary elimination. A third approach is empiric avoidance of the 6 most common food allergens in the United States (milk, egg, soy, wheat, peanut/tree nuts, fish/shellfish), without testing. Kagalwalla et al[57] first attempted this "6 food" elimination diet (SFED) in a retrospective study by investigating the response of 35 children with EoE placed on the SFED for 6 weeks in comparison with the response of 25 historical control patients with EoE undergoing elemental diet treatment several years earlier. In the SFED group, 26 of 35 (74%) experienced symptomatic and histologic improvement (<10 eosinophils/

HPF), with 10 of 35 (29%) achieving complete remission (0-1 eosinophils/HPF); in the elemental diet group, 22 of 25 (88%) experienced symptomatic and histologic improvement, including 14 of 25 (56%) achieving complete remission.[57] This retrospective study was not intended to establish superiority or noninferiority but rather to demonstrate proof of concept. In a follow-up retrospective review, food reintroduction was tested separately in 36 individuals, with a trigger identified in 32 patients (milk in 74%, multiple foods in 16%) and no trigger identified in four patients.[58]

Gonsalves et al[59] conducted a prospective (nonrandomized, uncontrolled) study of a 6-week SFED in 50 adult patients with EoE (>18 years old) that investigated the histologic response, symptom scores, and QoL. All the patients underwent PST for food allergens and aeroallergens, remained on PPI therapy during the study, and had both prediet and postdiet biopsy with comparison of symptom scores (validated measure) and QoL measures. Histologic responders (<5 eosinophils/HPF) then underwent systematic reintroduction of foods every 2 weeks, followed by repeated biopsy 4 weeks later. SFED reduced counts to <15 eosinophils/HPF in 37 of 50 (74%) and <5 eosinophils/HPF in 32 of 50 (64%), and dysphagia symptom scores improved in 47 of 50 (94%). Among the 32 histologic responders, 20 underwent allergen reintroduction, with a trigger food identified in all the subjects (60% wheat, 50% milk, 10% soy, 10% nuts, and 5% egg). However, of these 20 subjects, skin testing was a poor predictor of the response to food reintroduction.[59] This study was limited by a lack of randomization, lack of a control group, selection bias for patients willing to undergo dietary elimination, imbalance from dropout of those unwilling to undergo allergen reintroduction, and lack of APT.

Lucendo et al[60] evaluated the long-term effect of a SFED that involved avoidance of cereal grains (wheat, rice, corn), dairy, egg, seafood, legumes (including peanut), any nut or seed, and soy. They consecutively followed 67 adults in a prospective, uncontrolled study of a 6-week SFED, followed by sequential, single-food add-back with repeated biopsy at 6-week intervals to assess remission rate (<15 eosinophils/HPF). All the patients had prediet food-specific serum IgE measurement and PST performed. Lucendo et al[60] found that 49 patients (73%) had post-SFED counts of <15 eosinophils/HPF, including 37 of 49 (76%) with counts <5 eosinophils/HPF. All 49 SFED responders underwent reintroduction, with a single trigger identified in 36% of patients, two triggers in 31%, and three or more triggers in 33% (62% cow milk, 29% wheat, 26% egg, and 24% legumes), although the researchers noted poor concordance between allergen testing and the reintroduction outcome. Importantly, 15 of 49 patients maintained the diet for 2 years, including 4 patients who maintained it for 3 years; notably, all 15 remained in remission, which implicates a role for how dietary therapy can be used as a maintenance strategy.[60] Limitations of the study included lack of a control group, a small sample size, imbalance from patient dropout, use of a different variation of the SFED, and lack of APT and potentially limited applicability in a US population, given notable geographic differences that exist in food allergy.

Is a particular dietary approach superior? Two retrospective case series evaluated the various dietary strategies. Henderson et al[55] compared remission rates among elemental diet, SFED, and targeted elimination diet in 98 pediatric patients with EoE who were ≤21 years old and were drawn retrospectively from a multispecialty clinic at a large academic center. Remission (<15 eosinophils/HPF) was evaluated after dietary therapy and food reintroductions, and predictive values for both PST and APT were calculated. All the patients remained on PPI therapy. All three diets were effective in inducing significant histologic response. The elemental diet reduced mean peak eosinophils/HPF from 51 to 1, SFED from 77 to 3, and targeted elimination diet from 38 to 7. There were significant differences in the odds of remission between the elemental diet and SFED and between the elemental diet and targeted elimination diet but not between the targeted elimination diet and SFED. Poor NPVs were noted for milk, egg, soy, and wheat (40%-67%) on the basis of PST and APT.[55] Limitations of this study include that it was a nonrandomized, uncontrolled, and retrospective study, which prevented adequate head-to-head comparison of any particular modality, and that it had potential bias in terms of dietary assignment. However, this study clearly demonstrates the potential for multiple successful dietary management strategies.

To determine the effectiveness of 7 dietary styles in patients with EoE, Spergel et al[56] conducted a similar study in 941 pediatric (≤18 years old) patients with EoE evaluated between 2000 and 2011. The final diet analysis was done in 319 patients after complete food reintroduction and biopsy. This was also a nonrandomized, uncontrolled retrospective study. All the patients were skin tested, and predictive values of PST and APT were evaluated through single-food add-back followed by biopsy to assess a change from prediet to postdiet counts (remission defined as <1 eosinophils/HPF) and/or development of symptoms. All the patients underwent an 8-week prebiopsy PPI treatment. Seven diets were evaluated: empiric milk avoidance; empiric milk, egg, and wheat avoidance; classic SFED (milk, egg, wheat, soy, peanut, and shellfish); test-guided elimination; test-guided elimination plus empiric milk elimination; empiric milk, egg, wheat, soy, and meat avoidance; or a vegan diet. Milk, egg, wheat, beef, soy, and chicken were the most prevalent triggers, and only 38% of the 319 patients had a single trigger. The combined PST/APT approach had reasonable NPVs (87%-91% by food) except for milk (44%), but PPVs varied (17%-82%). Approximately 53% achieved remission for test-guided elimination and for SFED separately; 47% for empiric milk, egg, and wheat elimination; and 30% for empiric milk elimination alone. Test-guided diet elimination with empiric milk elimination resulted in a 77% response rate, as did empiric milk, egg, wheat, soy, and meat elimination.[56] These 2 options suggest consideration of a combined test-guided plus selected empiric elimination as an option and that response to empiric elimination may be accomplished with four foods as opposed to six foods. The study design prevented head-to-head comparison of dietary approaches, and there was potential for bias in assignment of therapy, similar to the study by Henderson et al.[55] However, the study also demonstrated the potential for combining multiple dietary management strategies. The present evidence, by study, for dietary treatment is summarized in Table IV.

MONITORING FOR DISEASE PROGRESSION

The definition of remission or successful treatment is not agreed upon and varies between <2 to <15 eosinophils/HPF, in

TABLE IV. Comparison of identification of dietary triggers and successful food reintroduction

			Foods*						
Study	N	Age (y)	Milk, %	Egg, %	Soy, %	Wheat, %	Peanut/tree nut, %	Fish/shellfish, %	Legumes, %
Gonsalves et al[59]	20	22-55	50	5	10	60	10		
Kagalwalla et al[57,58]	36	7.6 ± 4.3	74	17	10	26	6		
Lucendo et al[60]	42	17-57	62	26.2	14.3	28.6	16.7	19	23.8
Henderson et al[55]	26	0.9-22	65	40	38	37			
Spergel et al[56]	319	1-18	66.1	24.5	16.3	22.6	5.0	0	
Total†	442		64.0	22.2	15.4	24.9	5.9	1.8	

*Foods that cause changes in esophageal eosinophil counts on reintroduction; multiple foods were reintroduced in the same patient.
†Total percentages represent an average of all 5 studies.

addition to cessation of symptoms. Irrespective of the total esophageal eosinophil count, it is reassuring to see a dramatic improvement in symptoms and histology despite eosinophil levels remaining >15 eosinophils/HPF. Follow-up of patients with EoE should be frequent, and consideration should be given to repeated endoscopy at regular intervals. The optimal interval for office-based or endoscopic reassessment has not been studied, nor is there consensus of whether histologic remission alone is sufficient if symptoms are ongoing. In addition, no study has evaluated optimal duration of steroid or dietary therapy. Most experts recommend that, when dietary triggers are added back into the diet, endoscopy be performed within 12 weeks to assess any resulting histologic change.[1] Caution should be taken, however, with patients who experience significant symptomatic improvement, given that there are several studies that show discordance between symptom resolution and persistence of abnormal histology.[19,20] Therefore, symptom response alone is an insufficient marker of disease remission. Regular follow-up visits are advised to monitor progress with a specific therapy, including compliance and social support issues.

Long-term complications from EoE include esophageal strictures, esophageal trachealization, esophageal furrowing and narrowing, microabscess formation, food impaction, persistent and/or progressive dysphagia, and lamina propria fibrosis.[61,62] Esophageal remodeling associated with subepithelial fibrosis may affect up to 40% of individuals, and predictors of this process are not well identified, although there is evidence that the process is reversible with treatment.[35,63,64] The effect of undertreatment or inadequate treatment is unknown. Some patients, despite treatment, progress to long-term esophageal dysfunction. To date, there is no known association with malignancy directly from the presence of EoE.[1,6] Importantly, major patient-oriented outcome measures, eg, health-related QoL, remain poorly explored within EoE. Preliminary work indicates that QoL is significantly impacted, and EoE-specific QoL indices are emerging as potential tools. QoL issues in patients with EoE are distinct and potentially more devastating than those faced by the general food allergy community.[65-68]

THE ROLE OF THE ALLERGIST IN THE DIAGNOSIS AND MANAGEMENT OF EoE

The role of the allergist in the diagnosis and management of EoE includes (1) evaluating for and managing comorbid atopic disease(s) that may contribute to EoE (eg, aeroallergen-induced seasonal variation); (2) identifying allergic triggers and managing dietary avoidance; (3) determining whether a patient should be prescribed injectable epinephrine therapy, instructing a patient in its usage, and conducting office-based food challenges during the course of food reintroduction; (4) managing anti-inflammatory medications, including systemic or topical corticosteroids; and (5) educating the patient and/or family on the role and mechanisms of food triggers in EoE. Concerning dietary avoidance therapy, analysis of the data suggests that an elemental diet, SFED, or test-guided diet all can potentially result in symptomatic and histologic change, although these diets differ significantly in the number of potential foods eliminated and thus potential impact on QoL and nutrition.

Treatment recommendations

On the basis of review of the data and available options for treatment of EoE, we propose an algorithm for clinical management of EoE (Figure 1). It is reasonable to begin therapy with either topical glucocorticoids or dietary therapy, depending upon patient and/or family preference and possible history of responsiveness and/or resistance to these therapies. If opting for dietary therapy, then an elemental diet is an easier option to consider for patients within their first year or two of life and an empiric elimination diet or targeted diet for older children and adults. Some providers opt to start both diet and steroid therapy simultaneously; however, there are no data that evaluate whether single vs dual therapy is a superior approach. Therefore, both styles are considered acceptable options at present, although it is generally preferred to introduce one option or the other in the majority of subjects so that response specificity is certain. As more data on patient phenotypes emerge, this may clarify the choice among specific diet, steroid, or combination therapy. In addition, the use of TCS with selective elimination of common triggers that have poor test precision and slow resolution (eg, milk, wheat) should be further evaluated in controlled studies.

Reintroduction of food is a foremost concern in any dietary elimination strategy. Reintroduction can be based on patient-reported history of symptoms, endoscopic follow-up, and predictive indices from allergy testing. Four studies of the SFED showed similar histologic response rates (73%-81%), although causative foods were only identified in 40%-65% of patients. The three dietary therapy management styles are compared in Table V and provides a suggested order of reintroducing foods after a SFED for children and adults, separately, is provided. Analysis of these data suggests that it may be feasible to narrow the SFED to a 4-food elimination diet (milk, egg, wheat, and soy), given the limited evidence that peanut, tree nut, and seafood are associated with recurrence. Although no data exist pertaining to reintroduction with elemental diet, the aforementioned pediatric and adult reintroduction approaches are also reasonable. In the subpopulation

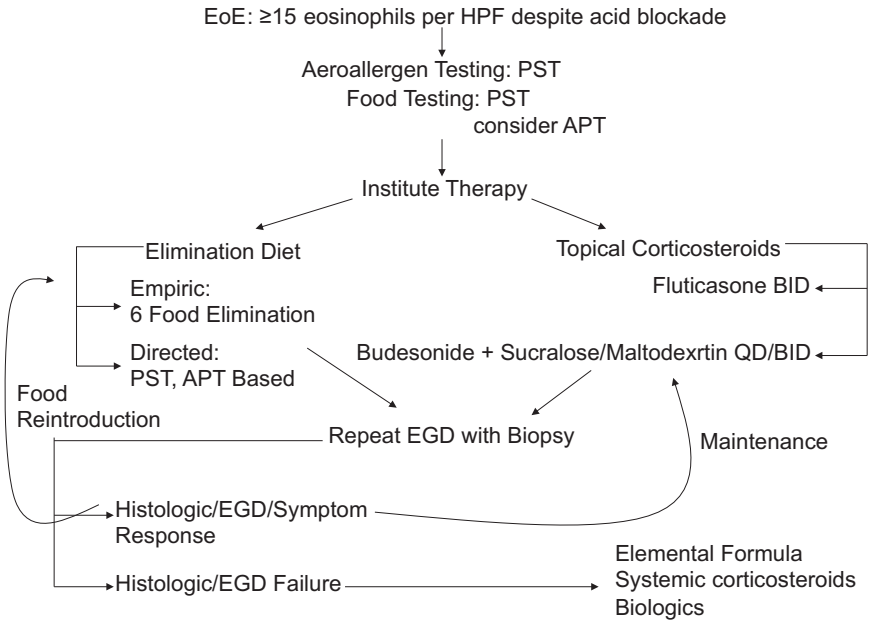

FIGURE 1. Schematic diagram of the recommended treatment algorithm for a patient with Eosinophilic Esophagitis.

TABLE V. Comparison of benefits and detriments of the three dietary management styles

Approach	Definition	Pros	Cons
Elemental diet	Diet exclusively consisting of amino acid–based formula	Hypoallergenic Nutritionally comprehensive Reduces symptoms and eosinophil counts	Taste (may require feeding tube) Expense Age appropriateness Excludes all food May have adverse impact on quality of life
Empiric diet	Diet that eliminates the major food allergens from the diet (typically milk, egg, wheat, soy, peanut/tree nut, and fish/shellfish, though variants exist)	Allergy testing not required Studied across all ages Reduces symptoms and eosinophil counts	Some avoidance may be unnecessary Only four foods may be necessary Expense May be nutritionally incomplete
Targeted diet	Diet that eliminates foods on the basis of allergy skin testing (skin prick test and/or atopy patch test)	Most specific therapy Can preserve diet Established sensitivity, specificity, and NLR/PLR to assist with add-back Reduces symptoms and eosinophil counts	Testing precision and technique is inconsistent across centers Milk testing precision very poor when negative Empiric milk elimination as an addition greatly improves response Some avoidance may be unnecessary (sensitization without clinical allergy)

Reintroduction strategy		Pediatric	Adult
Suggested order*	↓	Fish/shellfish Peanut/tree nut Soy Wheat Egg Milk	Fish/shellfish Egg Peanut/tree nut Soy Milk Wheat

NLR, Negative likelihood ratio; *PLR*, positive likelihood ratio.
*Data are best established for the classic "6 food" elimination diet but may be applicable to both elemental and targeted diets.

of patients with EoE that have coexisting symptomatic type I IgE-mediated food allergy, in-office oral food challenge may be necessary as part of the reintroduction strategy, and the decision to reintegrate these foods should be made carefully in conjunction with PST and serum-specific IgE testing. The value of these dietary approaches must ultimately be proven through large, multicenter, randomized, controlled clinical trials.

CONCLUSIONS

EoE is a clinicopathologic disease that has emerged as a major concern in the allergy and gastroenterology field. Symptoms are not a reliable surrogate of esophageal eosinophilia; patients in histologic remission can remain symptomatic, and, conversely, asymptomatic patients can have florid esophageal eosinophilia. The emerging diagnosis of PPIRee and its relationship to

PPI-resistant (classic) EoE is not yet known. EoE has a clear allergic etiology in the majority of patients, demonstrated by the predominant Th2 cytokine milieu and the response to dietary and corticosteroid treatment. Care of a patient with EoE is best comanaged by a multidisciplinary team with expertise in allergy, gastroenterology, pathology, psychology, and nutrition. Several therapeutic options exist, including two topical steroid options and three styles of dietary management. The natural history of disease is still somewhat unclear, including the long-term complications, influence of genetics and other risk factors, optimal duration of treatment, rates of relapse, and effect on QoL. Distinct phenotypes of EoE likely exist, which may help to explain the observed variability in presentation and treatment response, such as the recent observation that EoE may be associated with certain inherited connective tissue syndromes.[69]

Serum and esophageal biomarkers are emerging but are premature for clinical application. The practicing clinician must have a high index of suspicion for potential cases and should possess awareness for how to make the diagnosis as well as an understanding of the available treatment modalities.

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